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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/995,419	11/26/2001	Jim McWhir	096/004	1905

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	12

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,419	MCWHIR ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *16-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application filed November 26, 2001 claims benefit to provisional applications: 60/253,357, filed November 27, 2000; 60/253,443, filed November 27, 2000; and 60/253,395, filed November 27, 2000.

Applicants' amendment filed July 22, 2003, paper number 11, has been received and entered. Claim 14 has been amended. Claims 1-22 are pending.

Election/Restriction

Applicant's election with traverse of Group III in Paper No. 11 is acknowledged. The traversal is on the ground(s) that Groups I and III should not be restricted, and that they are drawn to the same inventive concept. It is argued that methods for lysing cells (group III) is a means to separate and deplete stem cells in the final step that are not wanted (claim 1), and that the two groups are linked by the inventive concept. This is found persuasive because Examiner agrees that the two groups represent linking claims as it is drawn to expressing a heterologous sequence wherein said expressed sequence is used to deplete undifferentiated cells. While the materials, methods and mechanisms for selecting an exogenously expressed cell surface marker are different than providing a specific cell complement to destroy the cell, each rely on detecting the exogenous cell surface marker. To this end, any means of selecting against a cell population expressing an exogenously expressed cell surface marker would be an obvious variation on the

inventive concept of expressing a transgene in an undifferentiated stem cell population and identifying stem cells by the expression of this transgene. Therefore, for the reasons above groups I and III are rejoined.

With respect to the election of species, it is noted that Applicants have elected a(1,3)galactosyltransferase and requested rejoinder of other cell surface antigens if claim 14 is found allowable (Applicants' amendment, page 6). As reasoned above, because the inventive concept of the claimed invention relies on the expression of an exogenous cell surface marker Examiner would agree that the species set forth in the claims and subject to restriction are obvious and not patentably distinct. Therefore, for the reasons above the election of species is withdrawn.

With respect to the restriction as it applies to the inventions set forth in Groups II, IV and V because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The requirement is still deemed proper and is therefore made FINAL.

Claims 1-22 are pending. Claims 16-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 16. Claims 1-15, drawn to a method of depleting undifferentiated stem cells from a population of cells comprising providing to a population of cells a heterologous polynucleotide comprising a promoter which is

expressed in a undifferentiated stem cell operably linked to a sequence which causes expression of a cell surface antigen and depleting undifferentiated cells from the population.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In this case, Applicants have elected methodology in which a heterologous gene is expressed. Since it is a heterologous gene, it must be introduced into the cell, therefore, claim 10 does not further limit claim 1 as it is drawn to the elected invention.

It is suggested that claims 1 and 14 be amended to encompass the elected invention and that claim 10 be canceled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15 and 5-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a differentiated cell by obtaining a

genetically altered undifferentiated stem cell comprising a heterologous construct that selectively expresses a cell surface antigen in an undifferentiated cell, differentiating said cells, an selecting for the cell surface antigen expressed, does not reasonably provide enablement for expressing post translational modifying enzymes such as glycosyltransferases, and identifying and selectively using complement to lyse said undifferentiated cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case, the basis of the rejection centers on the ability to provide and identify a specific antigen produced by the cell, and subsequently provide a specific complement to this antigen in order to lyse the cell. Examiner does not contest that any heterologous gene construct could be provided and could be expressed in a cell. Further, Examiner does not contest that a complement and its specific antigen present on the cell surface of a cell provided in the proper context and conditions would result in the lysis of the cell. The basis of the rejection focuses on the fact that simply providing an enzyme that functions to make post-translation modifications, in particular providing glycosysltransferases, at most results in a random modification of endogenous proteins. Given that the process results in random alterations, the specification fails to provide the necessary guidance to specifically define the 'specific antigen' that is produced. Consequently, not knowing the antigen present on the cell, the specification fails to provide the necessary guidance for the specific complement needed to practice the method. The specification fails to provide the necessary starting materials and guidance to practice the method as broadly claimed for providing and/or identifying newly formed antigens that are generated by post-translational modification. The courts have stated that: 'The written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics...i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of characteristics. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F 3d at 1324, 63 USPQ2d at 1613 (Fd Cir 2002). The scope of the claims is not

commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative embodiments.

One of the main considerations to be made in determining whether undue experimentation is required is the amount of experimentation required. See *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). As set forth in the decision of the Court: " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.'). Further, "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. "It is true . . . that a specification need

not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. In this case, the empirical nature of identifying potentially new antigens that are formed as a consequence of expressing an enzyme that provides post-translation modification, then subsequently, if a novel antigen is identified, producing a complement wherein said complement to said novel antigen lyses the cell would not be considered routine, encompassing an enormous amount of experimentation without any specific expectation of success.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 10, 11, 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 1 is vague and unclear because the method simply provides a genetically altered stem cell and depleting differentiated cells therefrom. It is unclear where or how the differentiated cells arise, since all that is provided is undifferentiated cells. More clearly indicating that differentiated cells are present in the starting composition or how they are provided in order to practice step (b) would address that basis of the rejection.

Claim 10 is unclear because it does not appear to further limit claim 14. Applicants have elected selecting against expression of a heterologous polynucleotide. Because the methodology requires that a heterologous gene is expressed, it must encompass introducing the polynucleotide into the cell. Claim 14 implicitly encompasses claim 10, and thus is not further limited by the method step.

Claim 11 is vague and unclear in the recitation of 'an endogenous transcriptional control element' because it is unclear if it is the endogenous element as it is found in the genome and the heterologous gene is inserted next to this control element, or that the transcriptional control element is from the cell but in the context of heterologous construct. If it is the latter, it is unclear what are the metes and bounds comprised by the term with respect to the specific

sequences required or functional aspects of such a control element one would need in order to consider the transcriptional control element to be considered 'endogenous'.

Claim 12 is indefinite in the recitation that P-X is transiently expressed. Initially, it is noted that Applicants have elected selecting against expression of a heterologous polynucleotide. Because the methodology requires that a heterologous gene is expressed, it must encompass introducing the polynucleotide into the cell. To that end, genetically altering the cell to provide a heterologous gene expression does not further limit the elected invention. Further, it is unclear what the metes and bounds for 'transiently' encompass and how it relates to the method of claim 14. Further, it is unclear how genetically altering the cell population is related to the transient expression. The claim is vague, unclear and confusing because the modification of altering the cell to transiently express the P-X is not adequately set forth. Upon review of the specification Examiner can not find any particular support or guidance for any specific promoter that is transiently expressed nor means to transduce cells to get transient expression in only undifferentiated cells.

Claim 13 is unclear and confusing in how the genetically altering the cell is related to be inherited or for specifically providing expression in an undifferentiated cell. Initially, it is noted that Applicants have elected selecting against expression of a heterologous polynucleotide. Because the methodology requires that a heterologous gene is expressed, it must encompass introducing the polynucleotide into the cell. To that end, genetically altering the cell to provide a heterologous gene expression does not further limit the elected invention. Further, the claim is

vague, unclear and confusing because the relationship of genetically altering, expression and specific inheritance of a particular cell population is not clearly set forth.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 14, 2-4, 9-10, 15 are rejected under 35 U.S.C. 102(e) as being anticipate by Smith *et al.* (US Patent 6,146,888).

Claim 14 is broad encompassing differentiating any type of undifferentiated stem cell wherein the cell comprises the structure P-X. It is noted that the claim as written is very broad and reads on differentiating any stem cell because any endogenous gene would have a gene with a P-X structure. However, because Applicants have elected that the sequence is heterologous, the claim is being interpreted to encompass a stem cell comprising a heterologous polynucleotide sequence. Additionally, it is noted that claims 14 and 15 do not require any selecting step, only differentiation. Claim 1 is being interpreted to be more narrow drawn to a method of producing a

cell population depleted of undifferentiated stem cells. It appears implicit in the claim is that the stem cells must be differentiated by some means, therefore is similar to the method of claim 14.

Smith *et al.* teach a method wherein a heterologous transgene is expressed in stem cells (column 2, lines 11-15). The heterologous construct taught by Smith *et al.* is one that comprises a promoter expressed in the stem cell and used to express a selectable marker. Smith *et al.* does not specifically state that it is P-X, but clearly the promoter-heterologous selectable marker constructs taught by Smith *et al.* anticipates the P-X set forth in the instant specification. Smith *et al.* teach a variety of markers that can be used both functionally and structurally, including antigens on the cell surface and other selectable markers (bridging columns 3-4). Smith *et al.* teaches a variety of promoters for expression in a stem cell including the use of the Oct promoter (see working examples), the endogenous promoter driving expression of the heterologous selectable marker (column 4, lines 52-63), and for the stable or transient expression of said promoters (column 4, lines 60-61). Finally, Smith *et al.* teach methods of differentiating cells including the reduction to practice the formation of embryoid bodies (columns 8-9 and see characterization of vectors in examples). It is noted that the preferred methods disclosed by Smith *et al.* focus on the isolation of stem cells such as by FACS sorting or immuno-selection of cell surface antigens, however in the isolation of stem cells the remaining population would be considered depleted of stem cells.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

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